In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 14-431V
Filed: November 23, 2016

* *	**PUBLISHED**
JANELLE and ARTURO ESCALERA, on behalf of their minor child, A.E.,	
Petitioners,	Special Master Hamilton-Fieldman
v.	Entitlement; Ruling on the Record; Diphtheria-Tetanus-acellular-Pertussis ("DTaP") Vaccine; *haemophilus* type B ("HiB") Vaccine; Celiac Disease.
SECRETARY OF HEALTH AND HUMAN SERVICES,	
Respondent.	
* *	

Andrew D. Downing, Van Cott & Talamante, PLLC, Phoenix, AZ, for Petitioners.
Christine M. Becer, United States Department of Justice, Washington, DC, for Respondent.

RULING ON ENTITLEMENT[1]

On May 20, 2014, Janelle and Arturo Escalera ("Petitioners") filed a petition on behalf of their daughter, A.E.,[2] pursuant to the National Vaccine Injury Compensation Program[3]. Petitioners alleged that the administration of diphtheria-tetanus-acellular-pertussis ("DTaP") and *haemophilus* type B ("HiB") vaccines on May 20, 2011 caused A.E. to suffer from celiac disease.

[1] Because this ruling contains a reasoned explanation for the action in this case, the undersigned intends to post this ruling on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). In accordance with Vaccine Rule 18(b), a party has 14 days to identify and move to delete medical or other information that satisfies the criteria in § 300aa-12(d)(4)(B). Further, consistent with the rule requirement, a motion for redaction must include a proposed redacted decision. If, upon review, the undersigned agrees that the identified material fits within the requirements of that provision, such material will be deleted from public access.

[2] The caption of the originally filed petition listed the minor child's full name. On June 25, 2014, the undersigned instructed the Clerk of Court to change the caption to reflect only the minor's initials.

[3] The Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-10 et seq. (hereinafter "Vaccine Act," "the Act," or "the Program"). Hereafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

Based on the medical records and expert reports, the undersigned finds that Petitioners are entitled to compensation under the Vaccine Act.

I. Procedural History

Petitioners filed two sets of medical records and an affidavit from Mrs. Escalera, followed by a statement of completion, on June 23 and August 12, 2014. *See* Petitioners' Exhibits ("Pet. Exs.") 1-3. On October 2, 2014, Respondent filed a Rule 4(c) Report ("Resp. Report") in which she recommended against compensating Petitioners for A.E.'s allegedly vaccine-caused injury. Respondent argued that Petitioners had failed to identify a medical theory that connects A.E.'s DTaP or HiB vaccinations to her celiac disease, and pointed out that none of A.E.'s treating physicians identified the vaccinations as causal. Resp. Report at 4-5. Respondent also argued that Petitioners' factual assertions regarding the onset of A.E.'s celiac disease—namely, that onset occurred on May 21, 2011, the day after vaccination—are unsupported by the record, and that A.E. may have had symptoms of celiac disease prior to vaccination. Resp. Report at 5-6.

At a Rule 5 status conference held on November 4, 2014, the undersigned noted that, in light of the lack of definitive contemporaneous medical records, A.E.'s pre-existing bowel distension does not appear to be a major obstacle to Petitioners' case. *See* Order, filed November 5, 2014, at 1. Respondent agreed with the undersigned's assessment and stated that her client's strongest concern is the lack of a medical theory causally connecting the vaccination to A.E.'s injury. *Id*. The undersigned instructed the parties to consider settlement; in the event that they were unable to informally resolve the case, Petitioners were instructed to file an expert report identifying a theory of causation. *Id*. at 1-2.

Respondent ultimately declined to informally resolve the case, *see* Respondent's Status Report, filed December 22, 2014, and Petitioners filed an expert report authored by Dr. David Axelrod on January 14, 2015. *See* Pet. Ex. 4. Petitioners filed supportive medical literature on January 19, 2015. *See* Pet. Exs. 6-21. Respondent filed her responsive expert report, authored by Dr. Stephen McGeady, on May 29, 2015; she filed supportive medical literature on May 1, 2015. *See* Respondent's Exhibit ("Resp. Ex.") A (expert report), B-H (medical literature).

At a status conference held on June 3, 2015, the undersigned and the parties discussed Dr. McGeady's argument that A.E.'s pre-vaccine bowel distension was a symptom of celiac disease. *See* Order, filed June 4, 2015, at 1. The undersigned directed Petitioners to file any additional evidence that might shed light on this issue, as well as a supplemental expert report. *Id.*

On August 12, 2015, Petitioners filed a letter, signed by a certified physician's assistant who primarily treated A.E. at her pediatrician's office, stating that "there [was] no indication by the notes or . . . memory that [A.E.'s] symptoms preceded the June 6, 2011 office visit." Pet. Ex. 23 at 1. Petitioners filed a supplemental expert report authored by Dr. Axelrod on June 25, 2015, as well as supportive medical literature. *See* Pet. Ex. 22 (supplemental report), 24-25 (medical literature).

A final status conference was held on May 10, 2016. *See* Order, filed May 11, 2016, at 1. During the status conference, both counsel agreed to forego an entitlement hearing in favor of a ruling on the existing record, and were ordered to notify chambers if their respective clients did not wish to proceed in this manner. *Id*. Neither party filed a notice requesting an entitlement hearing. Petitioners filed a Motion for Judgment on the Administrative Record ("Motion") on June 20, 2016;[4] Respondent filed a Response to Petitioner's Motion on July 25, 2016; and Petitioners filed their Reply on August 8, 2016.

This matter is now ripe for a ruling on entitlement.

II. Summary of the Relevant Evidence

a. Medical Records

A.E., the product of a normal pregnancy, was born without complication on January 17, 2010. Pet. Ex. 1 at 1; Pet. Ex. 2 at 1. Prior to the administration of the DTaP and HiB vaccinations on May 20, 2011, her medical history was unremarkable. *See generally* Pet. Ex. 2 at 41-101. A.E.'s childhood illnesses included upper respiratory and ear infections typical in children. *Id.* She received all routine childhood vaccinations. *Id.* at 1. According to Petitioner, A.E. had "no abdominal complaints" during her first fifteen months of life; "she was eating normal table food without complication." Pet. Ex. 1 at 1. On the day of the vaccinations in question, May 20, 2011, Petitioner reported no concerns to A.E.'s medical provider and it was noted that A.E.'s condition was "excellent." Pet. Ex. 2 at 38. The record also noted that at that time A.E. "[ate] well," taking both whole milk and table food. *Id.* Her abdomen was noted to have been "soft, non-tender, without masses," and with active bowel sounds. *Id*. at 40.

At 15 months old, A.E. was administered DTaP and HiB vaccinations. Pet. Ex. 2 at 38-39. According to Mrs. Escalera, A.E. became very fussy and seemed uncomfortable the day following her vaccinations, on May 21, 2011. Pet. Ex. 1 at ¶ 5. A.E.'s fussiness continued over the following days, prompting Mrs. Escalera to take her to the pediatrician for a sick visit six days after her vaccinations, on May 27, 2011. Pet. Ex. 2 at 36. At this visit, Petitioner reported fussiness, cough, and "possible ear problems." *Id.* A review of systems revealed no fever, no change in appetite, no nasal congestion, and no nasal discharge. *Id.* A cough was noted without shortness of breath, or wheezing. *Id.* A.E. did not "'appear' to have abdominal pain, no change in bowel movements, and [did] not 'appear' to have nausea [or] vomiting." *Id.* She was diagnosed with a cough and a rash and Petitioner was advised to return or call if symptoms persisted. *Id.*

According to Petitioner, thereafter, A.E. "started running a low grade fever" and was not herself. Pet. Ex. 1 at ¶ 6. "She was vomiting and having a lot of diarrhea." *Id.* Her stomach became distended. *Id.* A.E. was taken to the pediatrician about a week and half after her previous visit, on June 6, 2011. The record of this visit noted the chief complaint as: "low grade fever, fussy with fever, has not been acting herself for 2 weeks, denies coughing, congestion, vomiting, diarrhea, no known exposures, sleeps okay." Pet. Ex. 2 at 34. An examination

[4] Simultaneously, Petitioners filed six additional medical literature articles. *See* Pet. Exs. 26-31.

revealed a nourished and healthy appearance and an otherwise normal examination, but for "a lot of gas." *Id.* The examining physician assistant, Cathy Kelley, noted that A.E.'s stomach had been "distended in the past" so she ordered a comprehensive metabolic panel. *Id.* at 35. A.E. was diagnosed with a viral infection and abdominal pain at this visit. *Id.* In documenting a follow-up phone call that day, Ms. Kelley noted that she "spoke with mom—fever better but vomiting twice today." *Id.* at 33. Ms. Kelley noted that A.E.'s kidney and liver function tests were slightly abnormal, and that she would obtain an abdominal ultrasound. *Id.*

Petitioners aver that A.E.'s symptoms progressively worsened thereafter, prompting a trip to the emergency room. Pet. Ex. 1 at ¶ 7. A.E. was admitted to Phoenix Children's Hospital a week after her last pediatric visit for a two-week history of intermittent cough, decreased appetite, and a distended and hard abdomen. Pet. Ex. 3 at 264. During this visit on June 13, 2011, a low grade fever was observed, as well as irritability and difficulty sleeping. *Id.* A CAT scan of the abdomen showed nonspecific fluid around the heart, as well as evidence suggesting gastroenteritis, and a finding around her portal vein believed to "correlate with periportal edema or inflammation." *Id.* A chest x-ray confirmed a "mildly distended abdomen." *Id.* A.E.'s white blood cell count was high, notably with a high percentage of lymphocytes at 71 percent (normal range 15 to 40 percent). *Id.* Viral nasal swabs were negative and a blood culture showed no growth. *Id.* A.E. was diagnosed with a viral syndrome, viral myocarditis, and a benign heart murmur. *Id.* Dr. Anthony Ani noted in the discharge summary that "mom had always described her as having a full or mildly distended abdomen since early infancy." *Id.* at 265.

On June 22, 2011, A.E.'s father took her to the pediatrician's office for a follow-up visit for gastroenteritis. Pet. Ex. 2 at 30. Ms. Kelley noted that she had seen A.E. a week prior to this visit, and observed that her stomach was "very distended, so she sent [A.E.] to [Phoenix Children's Hospital emergency room]." Mr. Escalera reported that A.E.'s stools were pasty and that she had a bowel movement every day. *Id.* Ms. Kelley recorded that Mr. Escalera had a milk sensitivity and that there was no known family history of celiac disease. *Id.* Ms. Kelley diagnosed gastroenteritis and recommended that A.E. not receive milk for a week to see if it helped her symptoms. *Id.* She also noted that she would consider doing a celiac panel at A.E.'s 18 month well-check, if one was not completed before then. *Id.*

According to Mrs. Escalera, A.E. lost significant weight at that point in time and was continually having diarrhea and vomiting. Pet. Ex. 1 at ¶ 7. On July 6, 2011, A.E. was taken to the pediatrician's office for diarrhea over the previous 5 days. Pet. Ex. 2 at 27. Continued abdominal distention and decreased appetite were noted. *Id.* A gastrointestinal evaluation revealed a distended but soft abdomen, and a lot of gas. *Id.* Ms. Kelley referred A.E. to a gastroenterologist and ordered a celiac disease panel. *Id.*

A celiac panel performed on July 5, 2011 revealed "very highly elevated antibodies" for both anti-tissue transglutaminase IgA and gliadin IgA antibody. Pet. Ex. 3 at 230-31. The anti-tissue transglutaminase level was greater than 100, where a positive indication for celiac disease would be greater than 8, *id.* at 231, and her gliadin IgA antibody was also greater than 100, where a normal positive is a level greater than 17. *Id.* Dr. Emmanual Siaw remarked that this was a "very abnormal celiac serology panel," and that "she most likely has celiac disease though

this will need to be confirmed with tissue biopsy." *Id.* The plan was to schedule A.E. for an upper endoscopy with biopsies and disaccharidase assay as soon as possible. *Id.*

A.E. was taken to the gastroenterologist on July 14, 2011. *Id.* at 237. Dr. Siaw wrote:

> Her parents report that [A.E.] developed significant abdominal distention at about 1 year of age when she was transitioned to regular table foods. Her abdominal distention, however, has worsened significantly over the past 2 months, apparently, at one stage, her abdominal girth measured about 23 inches. She has also had diarrhea for the past 2½ months with loose-to-watery consistency stools multiple times a day. They have also noticed significant changes in her behavior over the past 1 month, as she is extremely fussy with low energy levels. Her appetite has also decreased significantly once again over the past 2 months, and she has lost weight significantly.

Id. Dr. Siaw recorded the family history as significant for irritable bowel symptoms in A.E.'s father, paternal grandfather, and paternal great grandmother. *Id.* at 238.

On July 16, 2011, A.E. was seen at Phoenix Children's Hospital emergency department for a 2 week history of watery diarrhea, as well as some vomiting. Pet. Ex. 3 at 164. Petitioner reported that over the previous 5 days, they tried to feed A.E. gluten-free foods, which improved her bowels until the day of admission, when her diarrhea resumed. *Id.* A 3 to 4 pound weight loss was noted. *Id.* A.E. was started on a regular diet at the hospital, and at the time of discharge, she had no further vomiting. *Id.* Abdominal imaging studies revealed "numerous air-fluid levels which also appeared to be within the colon area," suggesting colitis or a diarrheal illness. *Id.* at 165. Stool studies were negative for salmonella, shigella, campylobacter, shigatoxin 1 and 2, C.diff, and rotavirus. *Id.* at 102, 208-10.

An esophagogastroduodenoscopy and biopsies were performed on A.E. during a hospital admission on July 19, 2011. The results showed "marked flattening of the villi" in the duodenal area and a flattening of the mucosa of the duodenal bulb. Pet. Ex. 3 at 102, 150. Esophageal biopsies also showed mild esophagitis. *Id.* at 101, 150. These findings confirmed a diagnosis of celiac disease and she was started on a gluten-free diet on July 20, 2011. *Id.* at 220. Dr. Candice Yee noted that since starting the diet on the 20th up until her discharge on July 22, 2011, A.E. had no further emesis or diarrhea, and her abdominal distention improved, according to her mother. *Id.* at 101. A.E. was discharged from Phoenix Children's Hospital on July 22, 2011.

Over the course of the three months that followed, A.E.'s health improved on a gluten-free diet. On September 30, 2011, the gastroenterologist at Phoenix Children's Hospital noted that A.E. looked "significantly better than her initial clinic visit and was more interactive and playful." Pet. Ex. 3 at 78. Follow-up bloodwork on October 20, 2011, revealed an elevated anti-tissue transglutaminase antibody level at 33.57, and a deamidated gliadin IgG antibody level elevated at 149.12, with a normal range being less than 20. *Id.* at 87. At a pediatrician visit on October 10, 2011, it was noted that A.E. was doing well on a gluten-free diet and had "phenomenal" weight gain. Pet. Ex. 2 at 22. She was diagnosed with contact dermatitis and eczema at that visit. *Id.* A.E.'s gastroenterologists recommend a "strict gluten-free diet" for her

remaining life, and her parents are careful to keep her from gluten in food and cosmetics. Pet. Ex. 2 at 91; Pet. Ex. 1 at ¶ 9.

b. Expert Review

i. Qualifications of Petitioner's Expert, Dr. David Axelrod

Dr. Axelrod is a clinical allergist and immunologist at Allergy & Asthma Consultants, Inc. in York, Pennsylvania. Pet. Ex. 5 at 2. He received a medical degree from the University of Michigan Medical School in 1974. Pet. Ex. 5 at 1. Thereafter, he completed residencies in internal medicine at both the University of Toronto and William Beaumont Hospital. *Id.* Dr. Axelrod completed a fellowship in allergy, immunology, rheumatology, and medical laboratory immunology, and thereafter completed another fellowship in laboratory of clinical immunology at the National Institutes of Health. *Id.* He also served as a principal investigator in a laboratory tasked with the development of vaccines at the Walter Reed Army Institute of Research. *Id.*

Dr. Axelrod worked as an attending physician at William Beaumont Hospital in the Division of Allergy and Immunology, as well as the Division of Rheumatology. *Id.* at 2. In addition to research and clinical responsibilities, Dr. Axelrod worked in academia in various professorships at the Uniformed Services University of the Health Sciences, the Medical College of Ohio, University of Kentucky, the University of Medicine and Dentistry of New Jersey, and Oakland University-William Beaumont School of Medicine. *Id.* He is board certified in internal medicine, rheumatology, medical laboratory immunology, and allergy and immunology. *Id.* at 3.

ii. Qualifications of Respondent's Expert, Dr. Stephen McGeady

Dr. Stephen McGeady is an Emeritus Chief of the Allergy, Asthma and Immunology Division at DuPont Hospital for Children in Wilmington, Delaware. Respondent's Exhibit ("Res. Ex.") B at 1. He received a medical degree from Creighton University, Omaha in 1967. *Id.* He thereafter completed a residency in pediatrics at St. Christopher's Hospital in Philadelphia, and completed a fellowship in psychiatry and allergy at Duke University. *Id.*

Dr. McGeady has been on the faculty at Jefferson Medical College since 1974, and is currently a Professor of Pediatrics at this institution. Res. Ex. B at 1. He also served as the Director of the Allergy and Immunology Training Program at Jefferson Medical College for approximately eighteen years, and was the Medical Director of Children's Rehabilitation Hospital in Philadelphia for ten years. *Id.* at 2. He is currently the Emeritus Chief of the Allergy, Asthma & Immunology Division at DuPont Hospital for Children in Wilmington, Delaware. Dr. McGeady is board certified in pediatrics, allergy immunology, and diagnostic laboratory immunology. Res. Ex. B at 1, 2.

iii. Expert Opinions

1. Petitioner – Dr. Axelrod

Using the Miller criteria[5] to establish the plausibility of an environmental exposure as the cause of a disease, Dr. Axelrod opined that the DTaP and HiB vaccinations A.E. received caused her to suffer a fever, rash, and intestinal disease diagnosed as celiac disease. *See generally* Pet. Ex. 4. Dr. Axelrod found the temporal association between the vaccinations and symptoms, the lack of likely alternative explanations, the biological plausibility, as well as analogous reports of similar symptoms after receipt of the vaccines at issue, made it more likely than not the DTaP and HiB vaccines caused A.E.'s conditions. *Id.* at 2-6.

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[5] Miller et al established primary and secondary elements to assess the plausibility of assigning causality between an environmental exposure and the appearance of a disease. The primary elements are:

- Temporal association consistent with known biologic effects.
- Lack of likely alternative explanations.
- Dechallenge - did the defining aspects of the disorder disappear or improve when the exposure was removed.
- Rechallenge - did the disorder reappear or worsen when the exposure was reintroduced.
- Biologic plausibility - is the disorder plausible based upon the known in vivo or in vitro effects of the exposure.

The secondary elements are:

- Analogy - are there prior published or unpublished reports of a similar disorder developing after the exposure in question or after a similar exposure.
- Dose responsiveness - is there evidence that the dose or extent of the exposure is related to the likelihood of developing the disorder or to the disorder's severity.
- Specificity - are the defining symptoms, signs, and laboratory features of the disorder the same as those seen in previous cases after exposure to the same environmental agent.

According to Miller, the presence of 4 of the 8 attribution elements, with 3 of the 5 primary elements, is evidence for a causal relationship.

Pet. Ex. 4 at 2 (internal citations removed); *see also* Pet. Ex. 6.

Specifically, Dr. Axelrod proposed a two-part integrated theory of causation. First, he proposed that A.E.'s initial fussiness and a rash one week after the vaccinations were the result of the release of cytokines[6] in response to the vaccines. *Id.* at 2. Dr. Axelrod cited medical literature by Kashiwagi, Rochfort, Papdopoulos, Lawley, and Abbas, to explain the role of cytokines in the function of the immune system, and the resulting symptoms persons may experience as a result of elevated cytokine levels. *Id.* According to Dr. Axelrod, the Kashiwagi paper found that cytokines (Il-1b, Il-6, Tumor Necrosis Factor-a, and G-CSF) were detectable in subjects at 6 hours following vaccination and that the levels of those cytokines increased until 24 hours following vaccination. *Id.* The subjects of that study "presented with fever, presumably related to the cytokine release." *Id.* Rochfort showed that Tumor Necrosis Factor-a and Il-6 caused a disruption in the blood brain barrier, making it more permeable to "blood borne chemicals, such as cytokines, as well as adaptive immune antibodies and cells. . ." *Id.* Cytokines entering the central nervous system through the now-permeable blood brain barrier then act upon the nervous system and stimulate the production of more cytokines, which then create the same effect of increasing permeability of the blood brain barrier. *Id.* Papdopoulus found elevated levels of Il-6 were associated with the early phase of rash, and Lawley found that autoimmune cutaneous manifestations can occur from 10 to 25 days after the initial exposure to a foreign antigen. *Id.* The research in the Abbas textbook showed that "[i]f an individual had a prior exposure to an antigen (such as the influenza vaccine), then the expected clinical response would be expected to occur within a shorter period of time and with greater severity . . . ." *Id.* at 3.

Based on these articles, Dr. Axelrod theorized that A.E.'s DTaP and HiB vaccinations caused the release of cytokines, which facilitated release of additional cytokines into her central nervous system and thereby caused her to be fussy. Pet. Ex. 4 at 3. Further, Dr. Axelrod theorized that the rash A.E. developed 7 days following her vaccinations was consistent with the development of an immune complex rash, either as a primary immune response, or a memory immune response. *Id.* at 3. Dr. Axelrod found significant the fact that testing did not uncover infectious or structural etiologies for her symptoms. *Id.* at 4.

The second part of Dr. Axelrod's theory of vaccine causation was based on molecular mimicry between the pertussis and tetanus toxoid proteins and antibodies associated with celiac disease. Celiac disease is an immune mediated disorder of the small intestine and other tissues. Pet. Ex. 4 at 4. Gliadins, glutenins, secalin, hordein, and other related grains are implicated in this disorder, as these grains are known to be rich in glutamine[7] and proline[8]. *Id.* The enzyme, transglutaminase, interacts with glutamine and proline to allow processing of these molecules. *Id.* Where there is an anomaly in this process, tranglutaminase induces both an innate and

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[6] A non-antibody protein which acts as intercellular mediators, as in the generation of an immune response. DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 466 (32nd ed. 2012) [hereinafter DORLAND'S].

[7] A nonessential amino acid occurring in the juices of many plants and in some animal tissues. DORLAND'S, *supra* note 5, at 791.

[8] A nonessential amino acid which is a major constituent of collagen. DORLAND'S, *supra* note 5, at 1525.

adaptive immune response that causes the tissue damage associated with celiac disease. *Id.* Thus, in persons with celiac disease, the ingestion of grains rich in glutamine and proline stimulate an immune response, which is mediated by T-cells.

In support of his theory of molecular mimicry, Dr. Axelrod cited articles by doctors He, Makarova, Lammi, Facciano, and Luini. Dr. Axelrod acknowledged that Dr. He did not discover cross-reactive antibodies to the part of a gluten molecule known as a-gliadin. Pet. Ex. 4 at 5. However, Dr. Axelrod cited this study as evidence of homology between a-gliadin in gluten and an immunogenic protein of Bordetella pertussis, known as pertactin. *Id.* Dr. Axelrod cited Makarova on this point as well. *Id.* Additionally, he cited Lammi as having shown that T-cells in persons with celiac disease are both specific for and proliferate to deamidated gliadin, the resultant peptide once gliadin interacts with the enzyme transglutaminase. *Id.*

Another basis for molecular mimicry, according to Dr. Axelrod, involved homology between tetanus toxoid and the active sites of enzyme transglutaminase. *Id.* "Facciano and Luini have shown that the tetanus toxoid stimulates transglutaminase activity that is reactive to glutamine." *Id.* This research has also shown that a tetanus toxoid receptor, known as ganglioside GT1b, inhibits binding of gluten proteins to the enzyme transglutaminase; thereby prohibiting the breakdown of these proteins and freeing up the transglutaminase to interact with tetanus toxoid and stimulate an immune response. *Id.*

According to Dr. Axelrod, A.E.'s receipt of the DTaP and HiB vaccines caused her to develop both an antibody and cellular response to the components of her vaccines. Pet. Ex. 4 at 5.

> She developed what may have been an immune complex rash (given the timing described above), indicative of an activated immune system. This immune response also reacted to her tissue transglutaminases to participate in the development of her rash and to produce the inflammatory disease of her upper intestinal tract, that manifested as fever, abdominal pain, abdominal distension and vomiting. She likely developed further damage that left her with a gluten responsive Celiac Disease.

Id.

Dr. Axelrod noted reports of adverse events associated with the HiB vaccine, as discovered by Dr. Rinderknecht, which included rash, irritability, vomiting, diarrhea, and gastroenteritis. Pet. Ex. 4 at 6. Dr. Axelrod concluded his opinion by stating that A.E. met the biologically expected time intervals for an innate, primary, and memory adaptive response to the vaccines she received.

2. Respondent – Dr. McGeady

Dr. McGeady criticized Dr. Axelrod's use of the Kashiwagi paper in so far as Dr. McGeady believed the paper did not support the contention that the vaccines A.E. received caused her gastrointestinal symptoms and fussiness. Res. Ex. A at 3. Dr. McGeady

acknowledged that Kashiwagi found "increased production of a number of proinflammatory cytokines" in peripheral blood mononuclear cells exposed to "a number of vaccines in vitro." *Id.* However, Dr. McGeady found significant the authors' note that the results of the study may be affected by preservatives and stabilizers used in the vaccines. *Id.* Additionally, Dr. McGeady found it notable that the Kashiwagi paper reported testing of DPT vaccine whereas [A.E.] received DTaP." *Id.* He believed the whole cell pertussis component may have also influenced the results. *Id.* at 3, 4. Kashiwagi described no exact matches between the vaccines received in the study and those which A.E. received. *Id.* at 4.

Dr. McGeady noted that when the febrile and non-febrile groups in Kashiwagi's study were compared, only the glycoprotein, G-CSF, was significantly elevated in the febrile group of vaccine recipients, while all other cytokine levels were comparable. Res. Ex. A at 4. Dr. McGeady concluded that "since G-CSF is not known to cause celiac disease, it fails the test of "known biologic effect." *Id.* Dr. McGeady also posited that the Papadopolous paper referred to an urticaria rash, of which the medical records do not make specific mention in A.E.'s case. *Id.* He similarly challenged references to the Abbas textbook and the Miller paper which discussed the association of the production of antibodies and rash development in children, on the basis that "[he] could not find a rash described [in the medical records], so these references lend no weight to the claim of similar biological effect." *Id.* He also found the rash discussed in the Lawley paper as irrelevant to this case as it discussed a rash as part of an immune complex disease, whereas according to Dr. McGeady, A.E. had occasional rashes "but no rash resembling the distinctive palmar and plantar eruptions described by Lawley et al." *Id.* at 4. Nevertheless, Dr. McGeady acknowledged that A.E.'s assessments following receipt of the vaccines at issue do make several mentions of a rash. *Id.* at 4, 7.

Dr. McGeady agreed that A.E. was correctly diagnosed with celiac disease, but, according to Dr. McGeady, "it is not believed that celiac disease is caused or precipitated by the DTaP, Hib or any other vaccine." Res. Ex. A at 5. He states that while celiac disease is known to be caused by "an immunologically harmful reaction between the innate and adaptive immune system and gluten (primarily the gliadin fraction), the reaction seems to occur only in individuals with certain [genetic markers], and only in a percentage of those individuals" as well. *Id.*

With regard to the biological plausibility of Dr. Axelrod's theory, Dr. McGeady acknowledged that Dr. Axelrod cited papers [Pet. Ex. 15 and 16] describing the "currently accepted mechanism of immune injury in celiac disease," but notes that "neither makes mention of vaccine exposure being a trigger of such pathology." Res. Ex. A at 5-6. Dr. McGeady criticized the use of the He paper to support a connection between the vaccines and celiac disease, as he states this paper "denies any antibody cross reactivity between the gliadin peptide thought to incite celiac disease, and pertactin, the immunogenic component of B. pertussis. The undersigned notes, however, that Dr. Axelrod provided this understanding in his report when he stated ". . . He et al did not find cross reactive antibodies to a-gliadin . . . ." and then cited Makarova as evidence of homology between pertactin and gliadin. Pet. Ex. 4 at 5. Dr. McGeady agreed the Makarova paper demonstrated "a structural similarity between transglutaminases in animals and microbes such as B. pertussis," however he opined that the study made no claim of immunogenic cross reactivity. Res. Ex. A at 7.

Dr. McGeady agreed with Dr. Axelrod's contention of homology between tetanus toxoid and substrate sites of transglutaminase, based on the study of Facciano and Luini. Res. Ex. A at 7. However, he opined that this information only tangentially supported a connection between receipt of the vaccine and the development of celiac disease. *Id.* According to Dr. McGeady, "[s]ince the studies in this report were conducted with tetanus toxin and the vaccine contains a heat inactivated form of the toxin (toxoid) it is not even known that the vaccine toxoid has comparable biologic activity to tetanus toxin." *Id.* He further stated that "even if it were to be shown that toxoid did have similar activity, any relationship to celiac disease is unknown, and proposing such a connection is purely conjecture." *Id.*

In concluding his opinion, Dr. McGeady noted that a medical record from June 6, 2011 noted abdominal distention having been present in the past, suggesting that A.E.'s "symptoms of early celiac disease may not have started abruptly following the receipt of the vaccines on May 20, 2011, but may have been present for some time before that." Res. Ex. A at 8. He also proffered epidemiological studies which found no association between the DTaP vaccine and celiac disease or Type I diabetes mellitus (which sometimes occurs with celiac disease). *Id.* at 8-9.

3. Petitioner's Rebuttal Report – Dr. Axelrod

Dr. Axelrod explained that he used the Kashiwagi paper to postulate a connection between the injection of biologically active materials (such as vaccines) and fussiness, to the extent fussiness is a response of the central nervous system, just as fever was a response of the central nervous system in the subjects of the Kashiwagi paper. Pet. Ex. 22 at 1. Dr. Axelrod acknowledged that the measure of cytokines in the subjects of the Kashiwagi paper did not differ between the febrile and afebrile groups, however, he explained that generally fever does not result from the injection of a sterile needle without the injection of a biologically active substance. *Id.*

> It is the processing of the vaccines by the innate immune system that results in the release of these interleukins and then results in whatever communication events occur between the injection of the vaccine and the development of the fever. The fever represents an effect upon the Central Nervous System by the interleukins and other innate mediators that results in fever.

Id. Dr. Axelrod averred that if A.E.'s fussiness one day following receipt of the vaccines was the result of the injection of the biologically active materials, i.e. the vaccines, then the timing fits the timing described in the Kashiwagi paper. *Id.* He acknowledged that the Kashiwagi paper does not prove that A.E.'s fussiness resulted from the vaccine injections, nevertheless, he averred that it provided a theory and timing consistent with an innate immune response that occurred in A.E. as a result of her vaccinations. *Id.*

With regard to Dr. McGeady's suggestion that the whole cell pertussis vaccine may have accounted for the innate reactions measured in the Kashiwagi paper, Dr. Axelrod countered that Blatter et al showed that a Tdap (with acellular pertussis) injection resulted in fever, as did the whole cell injection in the Kashiwagi paper. Pet. Ex. 22 at 1. He further explained that the

Rochfort paper provided a theory for the entry into the central nervous system of innate and adaptive components of an immune response to vaccinations, which then cause fussiness in the subject. *Id.*

Dr. Axelrod acknowledged that we do not know the type of rash A.E. developed within a week of her vaccinations—whether it was Dermatitis Herpetiformis, which is associated with celiac disease, or an urticarial or eczematous eruption. Pet. Ex. 22 at 1. Nevertheless, he argued that all these types of rashes are skin reactions related to dilation of the blood vessels, which may represent an effect of cytokines, including interleukins. *Id.* at 2. Dr. Axelrod stated that the Papdopoulos paper provided a theory to explain that the rash A.E. developed may be due to the release of interleukin-6. *Id.* He further explained that

> [t]he rash that [A.E.] developed following her vaccinations may have represented an effect of her innate immune response to the vaccinations or from a primary adaptive immune response to her vaccinations. The diagram by Abbas shows that although the peak of a primary adaptive immune response occurs near 2 weeks following the primary exposure to antigen, the response is in progress by 1 week. This was the time frame at which [A.E.] developed her rash, following her vaccinations.

Id. (internal citations removed). In summary, Dr. Axelrod explained the first part of his theory as follows:

> [A.E] received her vaccinations, with the release of cytokines. These cytokines participated in her development of fever and rash. The timing of the rash is consistent both with the presence of Interleukin-6, as described by Papadopoulos and with the induction of an immune complex adaptive response (primary or secondary), as described by Lawley et al, Abbas and Miller et al. With the movement of both the innate and adaptive immune response facilitated by the released cytokines, she developed irritability, manifested as fussiness.

Id.

According to Dr. Axelrod, the second part of his theory on causation was based on homology. "Makarova et al found that Bordatella pertussis contains transglutaminase homologs. Immune responses to these structures would also respond to the tissue transglutaminases in [A.E.]'s intestine, to result in Celiac Disease." Pet. Ex. 22 at 2. A second basis for homology lies in tetanus toxoid's structural similarity to substrate sites of transglutaminases. *Id.* Additionally, a tetanus toxoid receptor, called ganglioside GT1b, inhibits binding to transglutaminase, which further bolsters the interaction of the toxoid with the transglutaminase. *Id.* at 3. Thus, the theory is that the immune response to the tetanus toxoid would respond to tetanus toxoid bound to transglutaminase. *Id.* Epitope spreading would allow an immune response to transglutaminase to persist even beyond dissipation of the tetanus toxoid, resulting in the development of celiac disease. *Id.*

Dr. Axelrod opined that A.E. likely had a biological predisposition to celiac disease, thereby causing her immune response to these homolog structures to rise to the level of celiac disease—whereas in the vast majority of the population, DTaP and HiB vaccines do not lead to the development of this condition. Pet. Ex. 22 at 3. He agreed with Dr. McGeady that the peer reviewed scientific papers he cited do not prove or disprove a relationship between the vaccines and celiac disease, but he believed they suggested a mechanism by which the vaccines could cause the condition. *Id.* To the extent A.E.'s symptoms began before the vaccination, Dr. Axelrod opined that the vaccines then would have aggravated an ongoing problem without having been the cause. *Id.*

III. The Applicable Legal Standard

Vaccine Rule 8(d) provides that "[t]he special master may decide a case on the basis of written submissions without conducting an evidentiary hearing." Vaccine Rule 8(d). During the status conference held on May 10, 2016, both counsel agreed to forgo an entitlement hearing in favor of a ruling on the existing record and neither party subsequently requested an entitlement hearing pursuant to the May 11, 2016 Order.

To receive compensation under the Vaccine Act, Petitioners must demonstrate either that: (1) A.E. suffered a "Table injury" by receiving a covered vaccine and subsequently developing a listed injury within the time frame prescribed by the Vaccine Injury Table set forth at 42 U.S.C. § 300aa-14, as amended by 42 C.F.R. § 100.3; or (2) that she suffered an "off-Table Injury," one not listed on the Table as a result of her receipt of a covered vaccine. *See* 42 U.S.C. §§ 300aa-11(c)(1)(C); *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006). Petitioners do not allege a Table injury in this case, thus they must prove that A.E.'s injury was caused-in-fact by an on-Table vaccine.

To establish causation-in-fact, Petitioners must demonstrate by a preponderance of the evidence that the vaccine was the cause of the injury. 42 U.S.C. § 300aa-13(a)(1)(A). Petitioners are required to prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321-22 (Fed. Cir. 2010) (*quoting Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)).

In the seminal case of *Althen v. Secretary of the Department of Health and Human Services*, the Federal Circuit set forth a three-pronged test used to determine whether a Petitioner has established a causal link between a vaccine and the claimed injury. *See* 418 F.3d 1274, 1278-79 (Fed. Cir. 2005). The *Althen* test requires the Petitioner to set forth: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* To establish entitlement to compensation under the Program, a Petitioner is required to establish each of the three prongs of *Althen* by a preponderance of the evidence. *See id.*

Specifically, under the first prong of *Althen*, Petitioners must offer a scientific or medical theory that answers in the affirmative the question "can the vaccine(s) at issue cause the type of injury alleged?" *See Pafford v. Sec'y of Health & Human Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004). This may be accomplished in a number of ways. "Reliability and plausibility of pathogenesis can be bolstered by providing evidence that at least a sufficient minority in the medical community has accepted the theory, so as to render it credible." *Id.* In addition, epidemiological studies and an expert's experience, while not dispositive, lend significant credence to the claim of reliability. *Id.* Articles published in respected medical journals, which have been subjected to peer review, are also persuasive. *Id.* However, publication "does not necessarily correlate with reliability," because "in some instances well-grounded but innovative theories will not have been published." *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 593–94 (1993).

In addition to showing that the vaccine at issue can cause a particular injury, a Petitioner must also prove that the vaccine actually did cause the alleged injury in a particular case. *See Pafford*, 2004 WL 1717359, at *4; *Althen*, 418 F.3d at 1279. A Petitioner does not meet this obligation by showing only a temporal association between the vaccination and the injury; the petitioner must explain "how and why the injury occurred." *Pafford*, 2004 WL 1717359, at *4.

While a temporal association alone is insufficient to establish causation, under the third prong of *Althen*, a Petitioner must show that the timing of the injury fits with the causal theory. *See Althen*, 418 F.3d at 1278. For example, if the Petitioner's theory involves a process that takes several days to develop after vaccination, an injury that occurred within a day of vaccination would not be temporally consistent with that theory. Conversely, if the theory is one that anticipates a rapid development of the reaction post-vaccination, the development of the alleged injury weeks or months post-vaccination would not be consistent with that theory. The special master cannot infer causation from temporal proximity alone. In fact, it has been held, that where a petitioner's expert views the temporal relationship as the "key" indicator of causation, the claim must fail. *See Thibaudeau v. Sec'y of Health & Human Servs.*, 24 Cl. Ct. 400, 403-04 (Fed. Cl. Oct. 23, 1991); *see also Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992); *Hasler v. United States*, 718 F.2d 202, 205 (6th Cir. 1983) (stating that inoculation is not the cause of every event that occurs within a ten-day period following it).

A Petitioner who demonstrates by a preponderance of the evidence that he suffered an injury caused by vaccination is entitled to compensation, unless the Respondent can demonstrate by a preponderance of the evidence that the injury was caused by factors unrelated to the vaccination. *See Althen*, 418 F.3d at 1278; *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 547 (Fed. Cir. 1994).

IV. Discussion[9]

a. *Althen* Prong One

Petitioners must offer a medical theory that answers in the affirmative "can the vaccine(s) at issue cause the type of injury alleged?" *See Pafford v. Sec'y of Health & Human Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004). Both experts agree that A.E. was correctly diagnosed with celiac disease.

Among the conclusions in the Kashiwagi study[10] was that:

> All effective vaccines induce the production of cytokines or chemokines, which modulate immunogenicity and are also involved in inducing adverse events, such as system febrile illness and immunotoxicity. In this standpoints, Il-6, Il-10, Il-12, G-CSF, IFN-y, and TNF-a were detected in both febrile and non-febrile groups after vaccination in comparison with those in normal subjects.

Pet. Ex. 7 at 9. The Kashiwagi findings provide a sound basis for Dr. Axelrod to opine that fever and fussiness can be induced by receipt of vaccines through activation of cytokines in an innate immune response. In the undersigned's experience, fever and fussiness is often seen in children in the days following receipt of vaccines. Dr. Axelrod provided the mechanism by which this well-known phenomenon occurs. Dr. McGeady's challenge to the Kashiwagi paper centered on the fact that the subjects received a whole cell pertussis vaccine whereas A.E. received acellular pertussis vaccine is addressed by the Blatter study, [11] which found that fever resulted in subjects receiving DTaP, s*ee* Pet. Ex. 24 at 6 (stating the symptoms of fever and fatigue occurred in both groups receiving vaccines containing acellular pertussis components), as did the Rochfort paper[12], established that cytokines increase permeability of the central nervous system to

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[9] The undersigned has reviewed all of the medical literature provided by the parties, but will only discuss the literature relevant to this ruling.

[10] Kashiwagi Y, Miyata A, et al., *Production of Inflammatory Cytokines in Response to Diptheria-Pertussis-Tetanus (DPT), Haemophilus Influenzae Type B (Hib), and 7-Valent Pneumococcal (PCV7) Vaccines*, 10.3 HUMAN VACCINES & IMMUNOTHERAPEUTICS 677-85 (2014).

[11] Blatter M, Friedland L, et al., *Immunogenicity and Safety of a Tetanus Toxoid, Reduced Diphtheria Toxoid and Three-Component Acellular Pertussis Vaccine in Adults 19-64 Years of Age*, 27 VACCINE 765-72 (2009).

[12] Rochfort K, Collins L, et al., *Downregulation of Blood-Brain Barrier Phenotype by Proinflammatory Cytokines Involves NADPH Oxidase-Dependent ROS Generation: Consequences for Interendothelial Adherens and Tight Junctions*, 9.7 PLOS ONE e101815 (2014).

additional cytokines, thereby causing fussiness in the subjects. *See* Pet. Ex. 8 at 1 (concluding that cytokines TNF-a and Il-6 downregulate the expression of interendothelial adherens and tight junction proteins in the blood brain barrier, "leading to elevation of paracellular permeability").

Petitioners' theory concerning A.E.'s rash is persuasive to the extent that it establishes further evidence of an ongoing innate immune response related to the release of cytokines. While Dr. McGeady points out and Dr. Axelrod acknowledges that the medical records do not specify the type of rash A.E. suffered, Dr. Axelrod does persuasively explain that regardless of the characterization of the rash, a skin reaction in the form of a rash can suggest dilation of blood vessels, which is a known effect of cytokines. *See* Pet. Ex. 22 at 1-2; *see also* Pet. Ex. 11 at 1[13] (stating the "major mediator for the urticarial reactions is histamine and possibly leukotrienes, proteases, kinines, TNF-a and GM-CSF).

The second part of Dr. Axelrod's theory regarding molecular mimicry is persuasively established by the medical literature, and even in part by Dr. McGeady's agreement that the Facciano and Luini study[14] found a homologous sequence between tetanus toxin and substrate (or active) sites of transglutaminase. Dr. McGeady also acknowledged that Dr. Axelrod's theory relies on the "currently accepted mechanism of immune injury in celiac disease." Res. Ex. A at 6 (referencing the Caja and Castillo studies cited by Dr. Axelrod). His criticism, however, rests in the fact that neither of these studies make mention of vaccine exposure being a trigger of such pathology. *Id.* Dr. Axelrod agreed that the studies make no specific mention of a vaccine trigger, but countered that these studies "provide data points to suggest a mechanism by which the vaccines could result in celiac disease." Pet. Ex. 22 at 3. The undersigned agrees with Dr. Axelrod's assessment. The standard in this Program is not scientific certainty that a given vaccine causes a pathology, but rather a theory of causation based on current scientific understanding to preponderantly establish that a vaccine can cause the injury alleged.

The Caja study[15] described the mechanism of injury in celiac disease as the activation of the innate and adaptive immune systems by a peptide contained in gluten, called gliadin. Pet. Ex. 16 at 1. Gliadins are rich in glutamine. *Id.* One set of gliadin peptides, a-gliadin 31-43, activates innate immunity mechanisms; and a different set of gliadin peptides, the immunogenic peptides, activate the adaptive immune response when modified by transglutaminase. *Id.* at 1-2. Transglutaminase modifies gliadin when it deamidates (or breaks down) glutamine found in gliadin, to ready the residual matter for processing. *Id.* In a susceptible individual, this interaction stimulates an adaptive immune response; specifically, T-cell activation specific for

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[13] Papdopoulos J, Karpouzis A, et al., *Assessment of Interleukins IL-4, IL-6, IL-8, IL-10 in Acute Urticaria*, 6.2 J. CLIN. MED. RES. 133-37 (2014).

[14] Facchiano F and Luini A, *Tetanus Toxin Potently Stimulates Tissue Transglutaminase: A Possible Mechanism of Neurotoxicity*, 267.19 THE J. OF BIOLOGICAL CHEM. 13267-71 (1992).

[15] Caja S, Maki M, et al., *Antibodies in Celiac Disease: Implications Beyond Diagnostics*, 8 CELLULAR & MOLECULAR IMMUNOLOGY 103-9 (2011).

deamidated gliadin, thereby causing the tissue damage found in celiac disease. *Id.* "During this process, B cells start to secrete antibodies against the trigger, gliadin, and various self-antigens." *Id.*

The role of the vaccines at issue, according to Dr. Axelrod, lies in homology between the Bordetella pertussis bacterium, pieces of which are found in the DTaP vaccine, and transglutaminase. This assertion is supported by the He[16] and Makarova[17] studies. *See* Pet. Ex. 17 at 1 (stating the peptide transglutaminase is "highly homologous to the internal sequence of pertactin, an immunogenic protein of Bordetalla pertussis); *see also* Pet. Ex. 18 at 1. Dr. He and cohorts did not find that human antibodies to the gliadin component of gluten cross-reacts with Bordetlla pertussis, or in other words causes these antibodies to recognize Bordetella pertussis as gliadin. *See generally*, Pet. Ex. 17. However, Dr. Axelrod did not propose cross reactivity as the mechanism of injury. He recognized that celiac disease is a T-cell mediated disease. *See* Pet. Ex. 4 at 5. Dr. Axelrod's theory was that the similarity in structure triggered the adaptive immune response seen in celiac patients. The He study provides that "the a-gliadin component of gluten was recently identified as primary initiator of the inflammatory response to gluten in [celiac disease] patients." Pet. Ex. 17 at 1. As such, it is logical to conclude that a component of the vaccine (acellular pertussis), which is "highly homologous" to the primary initiator of an inflammatory response in persons with celiac disease (gliadin), can trigger T cells to produce the inflammatory response thought to occur in celiac patients when acellular pertussis is present.

Dr. Axelrod provided a second basis for the interaction of the vaccines within the mechanism of celiac disease, which is based on the homology between active sites of transglutaminase and tetanus toxoid. Facciano and Luini found "two sequences of [tetanus toxin] showing homology with known substrate sites of the enzyme transglutaminase." Pet. Ex. 20 at 1. They found that tetanus toxin stimulates transglutaminase activity and that this effect is greatly increased in the presence of physiological concentrations of calcium and GTP (a transglutaminase regulator). *Id.* They also found that tetanus toxin binds to transglutaminase and activates its enzymatic activity. *Id.* at 4. According to Dr. Axelrod, immune response to [tetanus toxoid] would also respond to tetanus toxoid bound to transglutaminase in A.E.'s intestine, to result in celiac disease. Pet. Ex. 22 at 2; Pet. Ex. 4 at 5. Moreover, the receptor, ganglioside GT1B, which is activated in the presence of tetanus toxin, inhibits binding to transglutaminase, making more transglutaminase available to interact with tetanus toxoid. Pet. Ex. 4 at 5. In this scenario, although the amount of tetanus toxoid would dissipate after some time, Dr. Axelrod opined that epitope spreading would allow an immune response to transglutaminase to persist beyond the dissipation of the tetanus toxoid.

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[16] He Q, Viljanen M, et al., *No Evidence of Cross-Reactivity of Human Antibodies to a 33-Mer Peptide of the Alpha-Gliadin Component of Bordetella Pertussis Pertactin*, 23 VACCINE 3336-40 (2005).

[17] Makarova K, Aravind L, et al., *A Superfamily of Archaeal, Bacterial, and Eukaryotic Proteins Homologous to Animal Transglutaminases*, 8 PROTEIN SCIENCE 1714-19 (1999).

Dr. McGeady questioned the biologic comparability of tetanus toxin studied in the Facciano paper, and tetanus toxoid, the heat inactivated form of the toxin contained in the vaccine. Res. Ex. A at 7. The undersigned is persuaded that tetanus toxoid has sufficient biologic comparability to tetanus toxin for the purposes of analyzing Dr. Axelrod's theory, as the basis of using tetanus toxoid in a vaccine is that it confers immunity against tetanus toxin when injected. Dr. Axelrod's theory regarding tetanus toxoid's interaction with transglutaminase is supported by the medical literature and is persuasive.

Respondent and Dr. McGeady posited that the Institute of Medicine found no reports of celiac disease associated with the DTaP vaccine, and that the evidence available favored rejection of any connection. *See* Res. Ex. A at 8-9. However, the purpose of the Program is to allow a finding of causation "in a field bereft of complete and direct proof of how vaccines affect the human body," thus this argument in the face of Petitioners' theory is not persuasive. *Althen v. Sec'y of HHS*, 418 F.3d 1274, 1280 (Fed. Cir. 2005). The undersigned generally does not find persuasive epidemiological evidence submitted to show that an alleged vaccine injury cannot occur (*Althen* prong one), for several reasons. First, epidemiology is only as good as the statistics that support it. There are often problems with statistics involving vaccine administration and injury, including significant issues with over reporting, under reporting, and with inconsistent definitions of what constitutes an injury and of the time frame during which any alleged injury must occur to be included in the report. Second, any epidemiological study, no matter how robust, can only show that a particular injury has not occurred, or is rare, not that such an injury cannot occur.

Dr. Axelrod's two part theory is rooted in the medical literature. As a general matter, Dr. McGeady did not question the reliability and credibility of the studies Dr. Axelrod cited, he only questioned the conclusions Dr. Axelrod drew from them, and in some instances agreed with some of Dr. Axelrod's conclusions. The medical literature provided supported the various propositions Dr. Axelrod used to build a theory of vaccine causation. Accordingly, under *Althen* prong one Petitioners have established by preponderant evidence a medical theory connecting A.E.'s receipt of the DTaP and HiB vaccines to the fussiness, rash, and fever she experienced shortly after her vaccinations, and her later diagnosis of celiac disease.

b. *Althen* Prong Two

The determination of causation in fact under the Vaccine Act involves ascertaining whether a sequence of cause and effect is "logical" and legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994). The undersigned noted during the Rule 5 status conference that, in light of the lack of definitive contemporaneous medical records, A.E.'s pre-existing bowel distension does not appear to be a major obstacle to Petitioners' case. *See* Order, filed November 5, 2014, at 1. Respondent agreed with the undersigned's assessment and stated her strongest concern was the lack of a medical theory causally connecting the vaccination to A.E.'s injury. *Id.* Petitioner provided a theory which the undersigned found persuasive on *Althen* prong one.

Regarding *Althen* prong two, Petitioners argued that the environmental trigger, namely A.E.'s vaccination, served as a significant factor causing the loss of gluten tolerance precipitating her celiac disease. Motion for Judgment on the Record ("Motion") at 14. Petitioners stated "A.E.'s development of fussiness, rash, diarrhea, vomiting, and other symptoms of celiac disease fits the theory posed by Dr. Axelrod's expert reports," as her symptoms of celiac disease did not manifest before she received the DTaP and HiB vaccinations. *Id.* at 16. Respondent responded by stating that "Dr. McGeady points out that the cause or causes of celiac disease have been extensively researched" and that celiac disease is known to be caused by "an immunologically harmful reaction between the innate and adaptive immune system and gluten and only seems to occur in individuals with certain Class II HLA types." Response to Motion for Judgment on the Record ("Response") at 6. Respondent stated that numerous factors, such as lack of breast feeding, time of introduction of gluten, the amount and quality of gluten in the diet, intestinal infections, and intestinal microbiota, have been identified as possible triggers for the reaction that causes celiac disease," and that vaccines were not a known trigger. *Id.* at 6-7. This argument seems to acknowledge that, while genetic susceptibility to celiac disease is important, it is not self-actuating—it needs a trigger of some sort to result in disease development.

Petitioners did not deny that A.E. may have been genetically predisposed to celiac disease. Rather, they argued that A.E.'s genetic predisposition, coupled with an environment trigger in the form of vaccines, led to the development of celiac disease. Motion at 14. On this point, the medical records note a family history significant for irritable bowel symptoms in A.E.'s father, paternal grandfather, and paternal great grandmother. *See* Pet. Ex. 3 at 238.

Petitioners provided a letter from A.E.'s provider, Ms. Kelley, on the issue of when symptoms of celiac disease began. Ms. Kelley stated that "[u]pon reviewing [A.E.]'s records, there is no indication by the notes or [] memory that her symptoms preceded the June 6, 2011 office visit." Pet. Ex. 23. The medical records reveal that Petitioners reported to physicians that A.E. had a distended abdomen for some time prior to the vaccinations at issue, but that there was a marked increase in the severity of her symptoms in the two months following her vaccinations—consistent with Ms. Kelley's statement. *See* Pet. Ex. 3 at 237. A.E.'s parents contemporaneously reported that she suffered significantly worsened symptoms in the weeks after her vaccinations, requiring repeated trips to the pediatrician's office and the emergency department. *See* Pet. Ex. 3 at 237-40; *see also* Pet. Ex. 1. Based on the record, the undersigned finds that irrespective of the abdominal distention A.E. suffered prior to her vaccinations, her abdominal symptoms (including distension) following receipt of the vaccines were striking, and that the symptoms she suffered (weight loss, vomiting, diarrhea, significant fussiness, low energy, esophagitis, and gastroenteritis) were different in kind and more serious in nature than the preexisting symptoms. *See id.* at 237. In addition, Dr. Axelrod opined that to the extent A.E.'s symptoms began before her vaccinations, the vaccines would have aggravated an ongoing problem without having been the cause. Pet. Ex. 22 at 3. The undersigned agrees.

Moreover, Dr. Axelrod's theory of causation is more persuasive in light of the fact that A.E.'s celiac panel on July 6, 2011 (six weeks after her vaccinations) was noted by her treating physician as containing "very highly elevated antibodies" for both anti-tissue transglutaminase IgA and gliadin IgA antibody. Pet. Ex. 3 at 230-31. According to the medical records, the anti-tissue transglutaminase level was greater than 100, where a positive indication for celiac disease would be greater than 8. *Id.* at 231. Additionally, her gliadin IgA antibody was also greater than 100, where a normal positive is a level greater than 17. *Id.* Dr. Emmanual Siaw remarked that this was a "*very* abnormal celiac serology panel . . . ." *Id.* (emphasis added). The undersigned finds it significant that the results of A.E.'s celiac panel were characterized by her treating physicians as "very abnormal" and "highly elevated," as these physicians more than likely encounter celiac patients with some regularity and found A.E.'s results eye-catching. The fact that both A.E.'s transglutaminase level and her gliadin IgA antibody level were extremely elevated gives support to the argument that both the pertussis and the tetanus mechanisms postulated by Dr. Axelrod may have been working in concert to promote the stronger reaction. Moreover, studies for other likely causes of her symptoms were negative. *See* Pet. Ex. 3 at 102, 208-10 (stating stool studies were negative for salmonella, shigella, campylobacter, shigatoxin 1 and 2, C.diff, and rotavirus).

These findings, based on the medical records and expert opinions, demonstrate that Petitioners have met their burden on *Althen* prong two.

c. *Althen* Prong Three

Dr. Axelrod explained the temporal association as follows:

> [A.E] received her vaccinations, with the release of cytokines. These cytokines participated in her development of fever and rash. The timing of the rash is consistent both with the presence of Interleukin-6, as described by Papadopoulos and with the induction of an immune complex adaptive response (primary or secondary), as described by Lawley et al, Abbas and Miller et al. With the movement of both the innate and adaptive immune response facilitated by the released cytokines, she developed irritability, manifested as fussiness.

Pet. Ex. 22 at 2. Dr. Axelrod averred that if A.E.'s fussiness one day following receipt of the vaccines was the result of the injection of the biologically active materials in the vaccines, then the timing fits what is described in the Kashiwagi paper. *Id.* at 1. He acknowledged that the Kashiwagi paper did not prove that A.E.'s fussiness resulted from the vaccine injections, nevertheless he averred that it provided a theory and timing consistent with an innate immune response that occurred in A.E. as a result of her vaccinations. *Id.*

Petitioners argued that "the timeline of events has no break between the administration of the vaccines and A.E.'s development of symptoms" of celiac disease, thus Petitioners believed they satisfied the proximate temporal relationship prong of *Althen*. Motion at 19. Respondent

relied on the fact that the medical record suggested A.E. developed abdominal distention prior to her vaccinations as evidence of no temporal association between the vaccinations and her development of celiac disease. *See* Response at 7-8.

As previously discussed, there is persuasive evidence that A.E. suffered new and severe symptoms associated with celiac disease following her vaccinations, symptoms confirmed by diagnostic testing and the contemporaneous statements of Petitioners. On the date of vaccination, the provider noted that A.E. was eating table food, consuming whole milk, and appeared normally nourished. Pet. Ex. 2 at 38-39. It was also noted that she had normal appearing stools. *Id.* Within the two months following receipt of her vaccinations, A.E. developed watery and pasty stools, diarrhea, vomiting, and lost a considerable amount of weight. She was diagnosed with celiac disease about six weeks after her vaccinations. Petitioners have provided a persuasive medical explanation of how the vaccinations could have triggered celiac disease in A.E., the timing of which is consistent with the medical records. Additionally, Petitioners have provided a statement from A.E.'s primary provider, Ms. Kelley, attesting to their assertion that the symptoms seen after her vaccinations were not present prior to June 6, 2011. For these reasons, Petitioners have met their burden under *Althen* prong three.

d. Alternative Cause

Respondent has not proposed an alternative cause and asserted that she "defends this case on the basis that petitioners have failed to provide preponderant evidence to satisfy their burden [under the] *Althen* prongs." Response at 8. The undersigned finds to the contrary. Petitioners have provided preponderant evidence to establish that but for the vaccinations, A.E.'s celiac disease would not have been triggered and that the vaccinations were a significant factor in bringing about her condition.

V. Conclusion

For the reasons discussed above, Petitioners have established entitlement to compensation. This case will now proceed to the damages phase. A separate damages order will be issued.

IT IS SO ORDERED.

/s/ Lisa D. Hamilton-Fieldman
Lisa D. Hamilton-Fieldman
Special Master